

kinds of molecules can also work as recruiters. Double-stranded RNA, for example, directs the RNA interference machinery to specific sequences in mRNA and in DNA, and thereby regulates a form of gene silencing.

Signals typically are conveyed to recruiters and, as implied by the discussion thus far, not to the enzymatic machineries themselves. For example, the sugar galactose (which we'll call a signal) causes the inhibitor bound to Gal 4 (called Gal80) to dissociate from Gal4, thereby triggering recruitment of the transcription machinery. This rule (that signals go to recruiters) is not ironclad: during formation of germ cells in *Drosophila*, for example, the transcriptional machinery is turned off entirely, and it would seem proper to call this a form of regulation.

Despite our lack of a precise definition, there are uses of the word 'regulation' that are inappropriate. For example, let us say that RNA polymerase, once recruited along with whatever else is required for transcription, undergoes some conformational change as it begins to work — surely it does. But to call such a conformational change 'regulatory', without any evidence that such a step is subject to modulation by changing signals in the cell, is to embark on a trail of endless regress in which every event on a biochemical pathway can be called 'regulatory'.

This discussion has centered on 'activation', the imposition of specificity by recruitment. 'Repression', as we shall see in our next encounter, is often, especially in eukaryotes, another manifestation of recruitment.

References

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Q & A

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Were there any important influences on your perception of the practice of science?

In the late 1950s while I was at school in Cornwall I was fascinated by biology and attended a week-end course given by a far-sighted teacher, Dr. Frank Turk. In addition to the exciting novelty, at that time, of staying away from home, I learnt the value of being sceptical of perceived wisdom. Ostensibly the course was concerned with the geographical distribution of plants and animals but in actuality the major topic was continental drift. I discovered that Alfred Wegener had been consigned to the intellectual wilderness for nigh on 40 years but with the then recent interest in palaeomagnetism he was now becoming mainstream. Hypothetical land-bridges were subsiding to oblivion. Soon afterwards as an undergraduate I was supervised by Fred Vine, then a research student who was proposing the concept of sea-floor spreading, and learnt that science could be really exciting. And at that time the most exciting aspect of biology was DNA and its implications.

What, in retrospect, do you think was your most significant experiment? Probably just one single experiment determined

the course of my scientific career. I was a post-doc in Jim Watson's lab at Harvard and then, as now, one of my projects was an investigation into how transfer RNA was transcribed. At that time Dick Burgess had prepared some ultra-pure *Escherichia coli* RNA polymerase. Unfortunately this preparation — what we now call the core polymerase — had a serious drawback: it didn't work when presented with an undegraded bacteriophage DNA template. One afternoon, after many frustrating attempts to tickle this enzyme into action, I mixed it with a small amount of impure enzyme and discovered not only that was there now activity, but also that the two preparations were synergistic. From this sprung the notion that a cycling factor — the sigma factor — was necessary for accurate transcription initiation. And from then on my research path was set.

And were there any deviations?

From the starting point of the sigma factor the wheel of research has turned full circle. In the early 80s, with Horace Drew, there was the fascinating diversion of how DNA structure influences transcription. The subsequent pursuit of this topic with Georgi Muskhelishvili and Malcolm Buckle has finally shown how the distinct superstructures formed by supercoiled DNA can define the three-dimensional structure of promoter sites responsible for directing transfer RNA synthesis.

What do you enjoy most about science?

One of the most rewarding aspects of science is the companionship of fellow scientists — throwing ideas back and forth sitting beneath the mists in the hot springs of Saturnia, stumbling over snowshoes in the Apennines, crossing the snowfields above Aussois or enjoying the biergartens of Munich. Discussion of a common problem with a colleague is so often synergistic and results in many (usually too many)

possibilities for new experiments. I have been extremely lucky to have worked closely with so many talented people who have an immense enthusiasm and curiosity for understanding how biological systems work. What is true for an individual is also true for an institution as a whole. In my early days at LMB the open seminars discussing, for example, Francis Crick's wobble hypothesis and Fred Sanger's new sequencing protocols were a revelation and an inspiration. LMB remains an institution where usually someone somewhere can answer your most obscure question and, more importantly, produce stimulating suggestions. But conversely it is clear that whenever the will to discuss results and ideas openly falters the science inevitably suffers.

What is the best advice you've been given? Towards the end of my Ph.D. I was wondering what to do next and Sydney Brenner told me that I would have to leave the lab and go somewhere where people think differently to gain a broader perspective. He was absolutely right. As a post-doc the change in environment was tremendously stimulating and opened my eyes to a different culture of practising science. I always give my own students the same advice even though for them Cambridge is sometimes a difficult place to leave.

Apart from the science itself what else is especially rewarding about a scientific career? To see students mature, become independent scientists in their own right and then to follow their future success gives an immense satisfaction. Sometimes you can almost see the metamorphosis as a student makes their first real discovery and gains the confidence that they need.

Do you have a particular gripe about the way science is administered? My main concern is that group leaders are being distracted by more and more

time-consuming requests to complete seemingly irrelevant forms. An excess of bureaucracy is anathema to curiosity. Given that, for many, curiosity is the driving force of creative science, this seems a self-defeating development. To be fair, LMB has, so far, been spared the worst excesses of this creeping authoritarianism.

What advice would you give to scientific planners? In the UK, well-established and still productive scientists are still often put out to grass when they reach their nominal retirement age. It seems a tremendous waste that, in the present much vaunted knowledge culture, so much experience and understanding should be so arbitrarily discarded. Surely it would be far better to follow the example in the USA, where in many institutions scientists can keep their bench for as long as their minds remain agile? Ageism has no place in science.

What do you think a scientist needs most? One extremely important aspect of practising science is to have the time and space to think. I am extremely fortunate to have a family who understand that on occasions I can become so engrossed with a new idea or an intellectual roadblock that I am oblivious to all other inputs.

What advice would you give to a young scientist starting out today? Beware of being seduced by your own hypotheses, however elegant they may seem to you. Unless you believe that you've discovered the equivalent of the structure of DNA, Nature has probably evolved a more satisfying and an even more elegant solution. On the other hand, if you believe there is sufficient evidence for your favourite idea, however radical it may seem to others, keep faith with it.

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Quick guide

Amazon mollies

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What are Amazon mollies? The Amazon molly (*Poecilia formosa*; Figure 1) is a small, livebearing fish of the family Poeciliidae and is found in diverse freshwater habitats from the lower Rio Grande valley (USA) to Tuxpan in Northeast Mexico. Mollies of the genus *Poecilia* are mainly found in Central America and the USA, but have been introduced worldwide.

Why are they called 'Amazon' mollies? The species is named after the Amazons — an all-female tribe of warriors from the Greek mythology. The mythical Amazons used males from neighboring tribes to reproduce and killed their male offspring. Like the mythical Amazons, Amazon mollies come only as females. However, they don't kill their males, but simply do not produce them in the first place.

How can they do without males? They can't entirely. Amazon mollies reproduce through a process called sperm-dependent parthenogenesis (gynogenesis). They produce diploid eggs without meiosis and these eggs are pseudo-fertilized by the sperm of males of different, related species. The sperm are only used to trigger embryogenesis and do normally not contribute genetic information. Thus, the reproduction of Amazon mollies is strictly clonal.

How do they 'mate'? Mollies — like other members of the Poeciliidae, such as guppies — are livebearing and fertilization takes place internally. Thus, Amazon mollies need to trick heterospecific males into copulating with them. Three species are known to serve as sperm donors in the natural habitats: the Sailfin molly (*Poecilia latipinna*) in the USA and both the Atlantic molly